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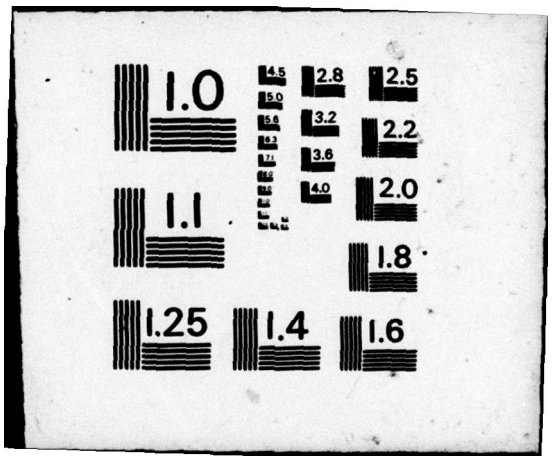
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Concerning the Mode of Infection in Epidemic Encephalitis

R. Inada*

Presse Medicale 45:386-387, 1937

(Translated by Phebe W. Summers)

Two hypotheses exist on the mode of infection in epidemic encephalitis: infection by the intranasal (IN) route and by the bite of a mosquito.

The first hypothesis, proposed by American scholars, has found some followers among us, for example Toniguchi. It was based on observations of experimental infection by the nasal route, in which, at autopsy, histologic examination of the brain revealed typical lesions. On the other hand the verification of virus in washes of the nasal cavity, even after filtration favors this hypothesis. Besides, an analogy exists between epidemic cerebrospinal meningitis and acute anterior poliomyelitis (infantile paralysis). Epidemiologic study shows that this illness rarely breaks out among members of the same family. Iimura (committee member) stated, in his report on epidemic encephalitis in 1933, that of 829 patients, there were only 4 families in which 2 members or more had contracted the disease at the same time. In last year's epidemic (1935) in Tokyo, Iguchi stated that in 1549 patients, 5 families only had counted 2 persons ill at the same time. This seems to indicate that contagion of the illness from man to man is rare.

We stop a moment here to consider what experimental studies have been carried out on the mode of infection of epidemic encephalitis are discussed. The recent study of the infection on animals showed us that outside of

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intracranial inoculation, and setting aside the conditions of human contamination, it is still intranasal inoculation which produces the highest percentage of morbidity, even compared to subcutaneous and intraperitoneal. All the committee members agree. In Takenouchi's (committee member) report, when virus inoculation is under the skin of mice, the virus is found in the blood 10 minutes after injection, the inoculated mice rarely contract the disease. Twelve hours after IN inoculation, virus is not found in the olfactory lobe, but at 24 hr the virus has multiplied to penetrate intracranially the olfactory lobe, starting an attack. The virus continues to multiply until it attains its maximum between 36 and 60 hr. In contrast the virus is not detectable in the cerebral lobe in the first 24 hr following IN inoculation; none is detectable after 30 hr. One finds virus in the blood, after IN inoculation a little after the time when virus begins to multiply in the cerebral lobe, i.e., after 48 hr. This supports the findings of Takenouchi, that inoculated virus in the nasal cavity reaches the olfactory bulb, multiplies, then invades the cerebral lobe. These findings are in agreement with those of which Webster and Fite reported on histologic brain lesions of mice inoculated IN. It is recalled that the lesions become visible on the 3rd day at the level of the olfactory lobe, extending on the 4th day to the piriform lobe and only arriving at the circumvolutions of the hippocampus on the 5th day.

Kobayashi (committee member) comes to the same conclusion that in mice on the 1st and 2nd days after IN inoculation, the virus is detectable only in the anterior portion of the brain and not in the posterior. After the 3rd day, the anterior portion is richer in virus than the posterior. Experimentation on the anterior third and the posterior third of the brain have given analogous results.

In summary, experimentatal IN inoculation gives, in comparison with other modes of infection, a high percentage of infection. It is evident that the virus penetrates the olfactory lobe and then extends into the cerebral lobe. But it seems to us that to be able to extrapolate purely experimental findings to natural human cases, there must be more experiments.

In 1933, at the first meeting of the committee, Mitamura suggested the possibility of spread by the bite of a mosquito or other insect, an hypothesis coming independently from the Americans. A little later Yamada, a specialist of the diptera, wrote to Okayama, stating that the epidemic had begun 2 weeks after development of the mosquitoes, and stated the hypothesis of a possible link between the disease and these insects.

Although there are other reasons to believe that mosquitoes are the vectors of the disease, I abandon these reasons to come more quickly to the experiments of transmission by mosquitoes.

It must be recognized that experiments of similar kinds were outlined in 1933 in the U. S. Leake, Musson and Chope (sic, probably Shope) had the idea of having mosquitoes bite an encephalitic and then placing them in contact with monkeys or mice. They used 3 species of mosquitoes: Aedes aegypti, Anopheles quadrimaculatus, Culex pipiens; but they did not reproduce the disease. They also tried to experiment on volunteer men, recruits in the penitentiary, but they failed to transmit the disease. This is why today in the U. S., mosquitoes are not considered the vectors.

Mitamura and Yamada proceeded somewhat differently; they had mosquitoes feed on patients and, after 4 weeks at ordinary temperature,

they placed them in contact with mice. The species of mosquito used was: Culex tritaeniorhynchus, (C.t.), the predominant species at Okayama and Culex pipiens var. pallens, most frequently encountered at Tokyo.

In 7 experiments with C.t. they transmitted the disease twice, once after 2nd passage, the other after the 6th passage. In 8 experiments with C. pipiens they produced the disease twice, once after the 3rd passage, once after the 4th. Until this the experimenters had tried to reproduce the disease imitating the mode of spread in nature, that is, injection into the brain of mice with homogenized whole mosquitoes which had bitten a patient. With C.t. one could reproduce typical encephalitis 3 of 9 times. The appearance of symptoms in these cases was noted twice after the 2nd passage and once after the 4th passage. In experiments with C. pipiens, disease was transmitted one of 7 times as early as the 2nd passage. The lesions in the brains of these contaminated mice were the same as in the typical case of encephalitis. It is not surprising that by injecting ground up mosquitoes into the brain of the mouse, the appearance of illness was more rapid, compared to the cases where infection was produced by infected mosquito bite.

Certainly, it would be preferable to transmit the disease to mice from the 1st passage; the appearance of the disease after several passages is inclined to remove these objections. Although, to settle the matter, transmission of the disease from the 1st passage would be more convincing, one can very well understand the difficulty of infecting by mosquito bite if one considers the small amount of virus in the blood compared to brain and the same means used for transmission. If one recalls that even in the case of injecting mice with infected human

brain, virulence of the virus attained a significant level after the 3rd or 4th passage, the results which just preceded seem sufficient to propose that the disease is transmitted by mosquito bite. It becomes easier to transmit the disease to mice if one removes the ground up organs of the infected mosquitoes and injects them into another mouse. If one proceeds in this way one successfully inoculates the disease after the 1st passage.

Recently, Webster, Clow and Bauer (J. Exp. Med. 6:April 1935) published a note on the presence of the virus of SLE in the body of Anopheles quadrimaculatus. Their technique is as follows: following IP injection of mice with the cerebral matter of an infected mouse, the virus can be demonstrated following a lapse of 5 hr postinjection. Then, they had mosquitoes bite this infected mouse 4 hr after virus inoculation. During the several days which followed they ground up some of the mosquitoes and injected these small amounts into the brain of other naive mice. They watched to see if these mice survived or died. Making use of A. aegypti, they found that this infected mosquito is virulent for 3 days. Using A. quadrimaculatus it was seen that this mosquito once infected is virulent until death. Its virulence is nearly 10,000 times the minimum dose able to infect the mouse by the cerebral route. It is curious therefore that this virulence decreases during the 2nd week to 100 times the infecting dose until even with the first and remains stationary for the remainder of life. Mice and monkeys bitten by these infected mosquitoes manifest no symptoms and are not immunized against the disease. Mitamura and Yamada, who concerned themselves with this question, have noted this rise and fall in virulence in infected mosquitoes.

All the facts accumulated by Mitamura and Yamada give evidence that mosquitoes are true reservoirs of the virus and can transmit the disease by biting laboratory animals. Although these experimental facts have incontestable value, can one conclude that epidemic encephalitis is transmitted to man by mosquito bite? Although the virus could, after a bite, not only invade the human body but initiate the disease, susceptibility ought to be a factor of primary importance. Since the mouse is very sensitive to the virus, transmission of the disease by mosquito bite is possible. But as in these cases, symptoms do not appear at first; they appear only after the 2nd, 3rd or 4th passage. It can therefore be said that the inoculum is in a very diluted state. Because the virus is diluted is it possible to give the disease to man? This is a difficult question to answer without new experimentation against epidemic encephalitis, man and monkey are nearly the same degree of sensitivity the latter being a little more receptive. One should make sure that the facts obtained in the mouse have the same value for the monkey. In other words, it would be more justified to experiment on monkeys before drawing conclusions for man. If the experimental monkey does not contract the disease, his blood could nevertheless yield information on the dose of virus it contains. Given that man is less sensitive than the mouse to epidemic encephalitis, it can be accepted that only under some conditions, in which its sensitivity increases, is disease contracted. Mitamura and Yamada are studying this question; but, since experimentation with mosquitoes is dependent upon the season, their work progresses slowly. It will probably not be before next summer that there will be new experiments on this subject.

To give more solid experimental bases to this hypothesis of mosquito transmission, it would be proper besides to consider the causes of the epidemic in the house of a patient, to collect mosquitoes there, grind them and inject them into mouse brain so as to know if they are carriers of virus. Unfortunately, it should be at the time of an epidemic; and this will not be possible until the next epidemic.

An objection can be given against this hypothesis of mosquito transmission; it rests with the fact that the number of patients in the cities is not in accord with the distribution of mosquitoes. Be that as it may, this hypothesis incontestably fits the experimental findings.

At the same time I have occasion to speak on the subject of epidemic encephalitis of Japan; there is, outside the epidemic encephalitis which rages in summer, another epidemic encephalitis which appears in winter. One might ask if for this winter disease the mosquito is always the cause and, if the mosquito is truly the cause, under what conditions does it survive the winter.

Another question would be to know where one can find the virus reservoir. We have at this time nothing very precise on this question but the epidemiologic facts, as Mitamura observed them. One tends to believe the ubiquity of the virus. According to this author, if certain meteorological conditions are met, the virus acquires the necessary virulence to attack man. But this is not the only theory which should be examined.